Remarks

Claims 1-7 and 15-22 are pending in the application. Claims 1-17 and 15-22 are rejected under 35 USC §103(a) as being unpatentable over Teicher et al. and Heath et al. Claims 17-22 are rejected under 35 USC 112, 1st paragraph, for lack of enablement. In order to expedite prosecution, Applicants hereby cancel Claims 1, 3-7, 16, 18, 20, and 22 while reserving the right to prosecute these claims in a continuing application.

First Rejection under 35 USC §103(a)

Claims 1-17 and 15-22 are rejected under 35 USC 103(a) as being unpatentable over Teicher et al. Applicants note that Claim 2 of the present invention relates to a specific polymorph of crystalline FB-HCl (wherein FB is as defined at p. 2. lines 1-5 of the specification). While Teicher et al. teaches that FB "can also exist as pharmaceutically acceptable acid addition salts," that "[a]cids commonly used to form such salts include inorganic acids such as hydrochloric…" and that "[p]articularly the hydrochloric and mesylate salts are used," only FB-2HCl was exemplified and tested.

Applicants assert that the claimed crystalline FB-HCI when considered as a whole, including its properties, is unobvious. For example, as pointed out in the specification (page 2, lines 15-18), FB-2HCl has been determined to be hygroscopic and poorly crystalline. Further, in solubility and stability tests, FB-2HCl exhibited profound precipitation prior to the first time point (6 days) in solutions held at 50 ^{0}C and at concentrations of up to 10 mg/mL. Moreover, at higher concentrations ($\geq$ 40 mg/mL) rapid precipitation was noted within minutes at normal room temperature (see specification at page 5, lines 5-12). This marked instability of FB-2HCI was a property thereof that caused applicants to abandon its clinical development.

In contrast, Applicants have surprisingly discovered that the claimed crystalline FB-HCl is capable of being reproducibly produced on a commercial scale, is not significantly hygroscopic, is sufficiently stable for use in oral formulations, and can be produced in a highly crystalline state (see specification at p. 2, lines 19-22; and p 5, line 26 to p. 8 line 13).

Since the significantly improved stability and crystallinity of the claimed compound, relative to FB-2HCI, could not have been predicted and since said improvements allowed for the clinical development of the claimed form, Applicants respectfully submit that the claimed invention is unobvious and request that the rejection be withdrawn.

Second Rejection under 35 USC §103(a)

Claims 1-17 and 15-22 are rejected under 35 USC 103(a) as being unpatentable over Heath et al. FB is exemplified in Heath et al., at Example 49. While FB is undoubtedly a very effective pharmaceutical agent, unexpected difficulties were encountered in its large scale production: unpredictable formation of THF-containing solvates complicated the commercial synthesis to such an extent that it became necessary to develop an alternate form for large-scale commercialization. (see specification at p. 2, lines 8-11; p. 5, lines 15-25).

In contrast, Applicants have surprisingly discovered that the claimed crystalline FB-HCl is capable of being reproducibly prepared on a commercial scale without THF-containing solvate contaminants. In addition, while *in vitro* solubility and dissolution data suggest that FB should offer bioavailability advantages in vivo relative to FB-HCl (see specification at p. 10, lines 1-2), Applicants have surprisingly discovered that plasma exposure in terms of area under the concentration vs time curves (AUC) for both 0 to 24 hr and 0 to infinity was significantly higher than that obtained for FB. (see specification at p. 10 lines 18-20). The increased exposure for FB-HCl was most likely due to increased bioavailability, since clearance did not appear to change given the similarities in apparent half-life of elimination values. (see specification at p. 10, lines 22-24)

Since these improved process and exposure properties could not have been predicted, and since said improvements allowed for the clinical development of the claimed form, Applicants respectfully submit that the claimed invention is unobvious and request that the rejection be withdrawn.

Rejection under 35 USC 112, 1st Paragraph for Enablement

Claims 17-22 are rejected under 35 USC 112, 1st paragraph, because the specification, while enabling for compounds and compositions, does not reasonably provide enablement for methods of treatment for the various diseases as claimed.

Whether an application satisfies the first paragraph of 35 U.S.C. § 112 depends upon whether the specification enables one of ordinary skill in the art to which it pertains, to make and use the invention without undue experimentation. In order to determine what constitutes undue experimentation in a given case, a standard of reasonableness must be applied, taking into consideration the nature of the invention and the state of the art. *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). There are many factors to be considered when determining whether there

is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to the following:

> (A) The breadth of the claims;
> (B) The nature of the invention;
> (C) The state of the prior art;
> (D) The level of one of ordinary skill;
> (E) The level of predictability in the art;
> (F) The amount of direction provided by the inventor;
> (G) The existence of working examples; and
> (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

In re Wands, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)

In applying this test, it is improper to conclude that a disclosure is not enabling based on an analysis of only one of the above factors while ignoring one or more of the others. For example, the fact that experimentation may be complex (as in drug discovery) does not necessarily make it undue, if the art typically engages in such experimentation. *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), aff'd. sub nom., *MIT v. A.B. Fortia*, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985). See also *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404. Rather, the Examiner's analysis must consider all the evidence related to each of these factors, and any conclusion of nonenablement must be based on the evidence as a whole. *Id* at 858 F.2d at 737, 740, 8 USPQ2d at 1404, 1407. A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993).

The MPEP (2701.03, IV.) makes it clear that method of treatment claims need not be supported by clinical data:

> Office personnel should not impose on applicants the unnecessary burden of providing evidence from human clinical trials. There is no decisional law that requires an applicant to provide data from human clinical trials to establish utility for an invention related to treatment of human disorders (see *In re Isaacs*, 347 F.2d 889, 146 USPQ 193 (CCPA 1963); *In re Langer*, 503 F.2d 1380, 183 USPQ 288 (CCPA 1974)), even with respect to situations where no art-recognized animal models existed for the human disease encompassed by the claims. *Ex parte Balzarini*, 21 USPQ2d 1892 (Bd. Pat. App. & Inter. 1991) (human clinical data is not required to demonstrate the utility of the claimed invention, even though those skilled in the art might not accept other evidence to establish the efficacy of the claimed therapeutic compositions and the operativeness of the claimed methods of treating humans).

Thus, while an applicant may on occasion need to provide evidence to show that an invention will work as claimed, it is improper for Office personnel to request evidence of safety in the treatment of humans, or regarding the degree of effectiveness. See *In re Sichert*, 566 F.2d 1154, 196 USPQ 209 (CCPA 1977); *In re Hartop*, 311 F.2d 249, 135 USPQ 419 (CCPA 1962); *In re Anthony*, 414 F.2d 1383, 162 USPQ 594 (CCPA 1969); *In re Watson*, 517 F.2d 465, 186 USPQ 11 (CCPA 1975); *In re Krimmel*, 292 F.2d 948, 130 USPQ 215 (CCPA 1961); *Ex parte Jovanovics*, 211 USPQ 907 (Bd. Pat. App. & Inter. 1981).

In addition, supporting evidence for method of treatment claims need not even be in the form of data from an art-recognized animal model for the particular disease or disease condition to which the asserted utility relates (MPEP 2107.03, III.) Rather, if reasonably correlated to the particular therapeutic or pharmacological utility, data generated using *in vitro* assays, or from testing in an animal model or a combination thereof almost invariably will be sufficient to establish therapeutic or pharmacological utility for a compound, composition or process. (MPEP 2107.03, III.). The correlation between particularly observed activity and the asserted therapeutic activity can be established, for example, by arguments or reasoning, documentary evidence, or any combination thereof.

Claims 17, 19 and 21 relate to methods of treating non-Hodgkins lymphoma, glioblastoma, and non-small cell lung cancer, respectively, in a mammal with crystalline FB-HCl of claim 2. In support of these claims, Teicher et al. describes efficacious treatment with FB-2HCl of rodents implanted with human T98G glioblastoma multiform and Calu-6 non-small cell lung carcinoma. (see WO 02/02094 at p. 12, line 1 to p. 14, line 20). The following references, relating specifically to the crystalline FB-HCl of claim 2, provide further support for claims 17, 19 and 21:

Nakajima et al., *Enzastaurin a protein kinase cbeta-selective inhibitor, inhibits the growth of SCLC and NSCLC cell lines*, Journal of Clinical Oncology, 2006 ASCO Annual Meeting Proceedings Part I, Vol 24, No. 18S (June Supplement) 2006: 13138

Fine et al., *Results from phase II trial of enzastaurin (LY317615) in patients with recurrent high grade gliomas*, Journal of Clinical Oncology, 2006 ASCO Annual Meeting Proceedings Part I, Vol 23, No. 16S (June 1 Supplement) 2005: 1504

Rossi et al., *The PKCβ selective inhibitor, enzastaurin (LY317615), inhibits growth of human lymphoma cells*, American Society of Hematology 2005 Poster Session 641-I: 1483

Robertson et al., *A phase II study of enzastaurin, a protein kinase c-β (PKCβ) inhibitor, in the treatment of relapsed diffuse large b-cell lymphoma (DLBCL)*, American Society of Hematology 2005 Poster Session 92-I: 934

Graff et al., *The protein kinase c b-selective inhibitor, enzastaurin (LY317615˙HCl), suppresses signaling through the AKT pathway, induces apoptosis, and suppresses growth of human colon cancer and glioblastoma xenografts*, Cancer Res., Vol. 65, No. 16, pp. 7462-7469 (August 15, 2005)

(see attachments)

In view of the this evidence, Applicants submit that claims 17, 19 and 21 are enabled and that, as a result, the rejection of claims 19 and 20-21 is improper and should be withdrawn.

Conclusions

In view of the foregoing amendments and remarks, Applicants respectfully submit that claims set forth an invention that is new, useful, and unobvious, and which is therefore deserving of patent protection. Passage to Issue of the present application is believed to be in order, and is respectfully requested.

Please charge any fees or credit any overpayment in connection with this application which may be required by this or any related paper to Deposit Account No. 05-0840.

If the Examiner has any questions, or would like to discuss any matters in connection with this application, he or she is invited to contact the undersigned at (317) 276-0307.

Respectfully submitted,

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